

# Why we still don't understand the depressed brain – Not going beyond snapshots

## Warum wir immer noch nicht die Vorgänge im Gehirn bei Depression verstehen, solange wir nicht über Momentaufnahmen hinausgehen

### Abstract

Although remarkable progress has been made in the search for the brain correlates of depression with neuroimaging methods, we still find a heterogeneity of results and lack of consensus. This short commentary proposes a theoretical reason for this situation linking it to the methods of conducting neuroimaging studies of depression and the ways to interpret findings. If we only take one snapshot of the “depressed brain”, the brain activity is presumably the result of four interacting components: neural predispositions, depressogenic pathology, changes caused by (chronic) depression, and compensatory brain mechanisms. The four components will be discussed briefly along with arguments why confusion of them might confuse our view of the brain in depression. After a short presentation of promising new longitudinal studies, this commentary gives first hints how we could go beyond snapshots to better understand the brain in depression.

### Zusammenfassung

Trotz bemerkenswerter Fortschritte in der Erforschung neuronaler Korrelate der Depression mit Methoden der Bildgebung finden wir immer noch heterogene Ergebnisse und eine mangelnde Übereinkunft. Dieser kurze Kommentar schlägt eine theoretische Begründung für diese Situation vor, die mit der Durchführung von Studien in dem Bereich und der Interpretation der Ergebnisse zusammenhängt. Wenn wir lediglich eine Momentaufnahme des Gehirns bei Depression machen, kann die gemessene Hirnaktivität das Ergebnis vier verschiedener interagierender Komponenten sein: neuronale Veranlagung, depressiogene Pathologie, Veränderungen, die durch (chronische) Depression ausgelöst werden und kompensatorische Hirnaktivität. Diese vier Komponenten werden kurz dargestellt – verbunden mit Argumenten, weshalb eine Verwechslung dieser unsere Sicht des Gehirns bei Depression verzerren könnte. Nach einer Darstellung vielversprechender neuer Längsschnitt-Studien gibt dieser Kommentar erste Hinweise, wie wir über Schnappschüsse hinaus gehen könnten, um das Gehirn bei Depression besser zu verstehen.

### Why we still don't understand the depressed brain – Not going beyond snapshots

One promising approach to study depression is the use of neuroimaging methods. Key questions throughout all research efforts are what the depressed brain looks like, what it actually does when depressed, and how we can help it from the “outside” to get better. Those questions primarily guide the investigation of morphological abnormalities, dysfunctional brain circuits, and research of

neurobiological medication effects, respectively. Within this perspective, depression is implicitly conceptualized as the structural or functional disturbance of an organ – the brain – just like the liver is affected in cirrhosis. Many years of neurobiological depression research have seen improved methods, smart study designs, increasing sample sizes, but instead of converging knowledge, the outcome has been a surprising heterogeneity of results with the eventual lack of clear answers to the questions above.

Well-conducted studies and thorough reviews allowed to list the brain areas suspected to show functional abnor-

**Henrik Kessler**<sup>1,2</sup>

**Harald Traue**<sup>3</sup>

**Daniel Wiswede**<sup>4</sup>

1 Universitätsklinik für Psychosomatische Medizin und Psychotherapie, Ulm

2 Universitätsklinik für Psychiatrie und Psychotherapie, Bonn

3 Universitätsklinik für Psychosomatische Medizin und Psychotherapie, Sektion Medizinische Psychologie, Ulm

4 Allgemeine Psychologie II, FSU Jena, Institut für Psychologie

malities in depression (amygdala, basal ganglia, prefrontal cortex, anterior cingulate cortex, etc.) but there is still no consensus regarding the direction of the changes in activation, nor the hemisphere in which these changes are most prominent [1], [2], [3], [4], [5]. More recently, network accounts of depression have interpreted the disease in the context of dysregulated neural circuits. One prominent approach conceptualises a dysfunction in the medial prefrontal cortex resulting in disinhibition of limbic transmission through the amygdala to visceral control structures and others leading to the endocrine, autonomic, cognitive and emotional manifestations of depression [6]. Another meta-analysis found limited overlap between studies investigating brain changes in depression with different paradigms (e.g. resting state, treatment effects, emotional activation studies): prefrontal cortex, anterior cingulate cortex, insula and superior temporal gyrus were found to be relatively hypoactive, whereas several limbic, subcortical and frontal regions showed hyperactivity [7]. In terms of volumetric changes in depression, a recent meta-analysis showed convergent gray matter volume reductions in anterior cingulate, orbitofrontal and – to a lesser extent – prefrontal cortex [8]. Additionally moderate volume reductions could be found in hippocampus, putamen and caudate nucleus [8].

Taken together, the heterogeneity across results and the lack of practical conclusions is still evident. It is consequently not yet possible to make clinically relevant statements about a depressed patient based on neuroimaging data, whereas physicians are able to base treatment decisions about a patient with cirrhosis on proper liver imaging diagnosis.

We propose that there are methodological and theoretical reasons why we still don't understand the depressed brain in order to really diagnose and treat patients based on neuroimaging methods, along with clinical and psychometric assessments. First, there are methodological differences and controversies about the imaging techniques, the approaches to data analysis and the interpretation of the results. Since these methodological issues have been well discussed elsewhere [9], [10], [11], [12], we will focus on one theoretical aspect in this commentary. The depressed brain itself, like any other organ, can be considered as a system with many variables interacting in such a way that the simple “snapshots” we take when collecting neuroimaging data may not be adequate to capture the way it functions.

Already more than ten years ago, David Lewis wrote in an editorial about brain changes in schizophrenia that any given brain alteration can represent three different phenomena: it can be the cause of a psychiatric disorder, its *consequence* or simply a means of the brain to *compensate* the disorder [13]. Unfortunately though, this fresh view was rarely considered when interpreting neuroimaging results in following studies. One aim of this commentary is thus to revive the discussion of possible interpretations of brain changes in depression incorporating recent literature. In our view, when we take a

neuroimaging snapshot of the brain at any given point in time of depression, the image is presumably the result of four interacting components: neural predispositions, depressogenic pathology, changes caused by (chronic) depression, and compensatory brain mechanisms. If the imaging data is only collected once, it is difficult to disentangle these four elements, what came first, what are the causal relations, what is central or just an epiphenomenon, in other words: what is the individual history of this depressed brain? The four components will be discussed briefly, followed by a short presentation of studies using promising longitudinal designs and finishing with a suggestion how to go beyond snapshots in the future.

## Neural predispositions

By “neural predispositions,” we mean the ways in which the (healthy) brain typically reacts to environmental stimuli, but which increase the possibility that it develops a depression. Although there is a wide array of studies considering normal brain processes triggered by emotional or cognitive stimuli, only some of these processes have been linked to depression. Probably the most important finding associated with the eventual development of depression is amygdala reactivity to emotional stimuli [14], [15] and decreased amygdala-frontal connectivity [16]. One further candidate for a neural predisposition to depression in healthy subjects is frontal EEG asymmetry. Following a diathesis-stress model, a reduced left relative to right activation has been proposed as moderating an affective style which predisposes for depression [1]. The main problem here is the lack of prospective studies linking right frontal lateralisation and the eventual development of depression in single subjects.

## Depressogenic pathology

These terms cover the brain changes that are thought to (immediately) cause depression. This is the most obvious and intuitive way to interpret brain imaging results in depressed patients. Popular models of depression, like limbic-cortical dysfunction [3] or reduced activity in anterior cingulate cortex [17], [18] follow this line of interpretation. We suggest, however, that the large amount of evidence apparently supporting this view could be more the result of a specific way of interpreting data, rather than a real outcome of findings. The fact that most of these results could also be interpreted as neural predispositions, changes caused by depression or compensatory brain mechanisms actually sparked off this commentary. Additionally, different subtypes and clinical manifestations of depression may be caused by different brain mechanisms. To our knowledge, none of the studies published so far has categorized patients in a clinically relevant way to interpret imaging results meaningfully.

## Changes caused by depression

This is the opposite way to interpret findings: chronic depression leads to brain changes. Sustained pathological processes associated with depression (i.e. hormonal) cause morphological (or functional) brain changes. The reduction of hippocampal volume in depression [8], [19], [20], [21] is one result we interpret along this line, considering two previous findings. First, hippocampal neuroplasticity is highly sensitive to elevated cortisol levels [22]. Since depression is commonly associated with high cortisol levels [23], this could be the mechanism through which depression has influence on the hippocampus. Second, a meta-analysis showed that volume reduction in the (right) hippocampus is correlated with the total number of depressive episodes suggesting that recurring depressions further reduce hippocampal volume [21].

## Compensatory brain mechanisms

“Compensatory brain mechanisms” are the countermeasures the brain uses to cope with depression. In our opinion, this is a promising way to look at the depressed brain and to interpret imaging data, though it has often been neglected. Since some brain activity associated with depression, like EEG asymmetry, can also be found in healthy participants [24], this activity could reflect an augmentation of existing circuits to (unsuccessfully) cope with the disease. Another argument supporting this new line of interpretation comes from psychotherapy research. One key factor in clinical improvement is the patients' ability to cope with the disease and to make use of therapeutic interventions [25]. If the patient has such an active role in his fight against depression, why not interpret brain imaging data as showing the neural substrate of this activity, e.g. emotion regulation? Clinical improvement in depression may primarily be a function of compensatory mechanisms inherent to the individual brain. The role of therapeutic interventions may therefore be, simply put, to trigger and sustain those mechanisms. One example for an interesting exception is the study of Norbury and colleagues where increased activity in dorsolateral prefrontal cortex in patients with a history of depression is interpreted as a correlate of more effortful emotion regulation after recovery from depression [26]. The weakness of many of the “classical” approaches to interpret findings is their assumption of linear relations within the brain. Recent models of the brain, though, conceptualize it as a network with modules interacting in complex (e.g. reciprocal) ways [27]. This position has already been discussed in the field of neurobiological aspects of psychotherapy [28]. In this view, depression is not a disorder localized in a single brain area but rather involves complex interactions between at least two major components: a dorsal (e.g. neocortical) and a central (e.g. subcortical) component. One of the conclusions of this network theory could explain the well-known fact that brain disturbances in different areas can lead to compar-

able dysfunctions, since they form distinct parts of a network involved in the disturbed function [28].

## Promising approaches using longitudinal designs

The statement of heterogeneity due to probable misinterpretations of results so far has focused on the vast majority of studies investigating the brain at one given moment. There is, however, a growing number of studies using longitudinal designs in the search for neurobiological treatment effects in depression. Those studies could contribute to disentangle the four components mentioned above and thus merit further attention.

One promising approach is the use of neuroimaging to predict treatment outcomes. The study of Siegle and colleagues is one such example, where better treatment response after cognitive behaviour therapy in depressed individuals was predicted by elevated amygdala and reduced subgenual cingulate (BA 25) activity when confronted with negative emotional words before treatment [29]. The authors conclude that those patients with the most prominent deficits in emotion regulation, as reflected by this neural pattern, could have the most benefit from an intervention that focuses on regulation strategies. In a recent study with severely depressed patients, Keedwell and colleagues showed that increased activity in right visual and subgenual cingulate cortex as a response to sad facial stimuli predicts better treatment response to antidepressant medication [30]. It is of note that the disparity between the two studies by Siegle and Keedwell could be explained by the assumption that psychotherapy and medication have an effect on different components of the cortico-limbic-subcortical network presumably involved in depression. Differential treatment effects of cognitive behaviour therapy versus medication have already been shown before [31]. Using volumetric rather than functional measurements, Frodl and colleagues reported an association between increased left anterior cortex volumes and better clinical outcome (less hospitalisations) in a large group of depressed individuals [32]. Of the relatively large number of longitudinal studies investigating treatment effects of medication on brain activity, only two shall be highlighted in the context of this short commentary. One fMRI study with depressed patients found hypoactivity in dorsolateral prefrontal cortex in a cognitive task with emotional interference, possibly reflecting reduced capacities to exert control over emotional interference [33]. Interestingly, this pattern was no longer found in patients after eight weeks of antidepressant treatment. The authors conclude that reduced emotional control capacities could have been restored by antidepressant treatment. In the study by Robertson and colleagues, eight weeks treatment with bupropion XL in patients with depression resulted in clinical improvement and attenuation of limbic responses to an emotional oddball task [34]. The significance of this effect is further supported by the fact that changes in amygdala activation

correlated with clinical improvement in terms of depressive symptoms.

Regarding treatment effects of psychotherapy on brain function, the evidence is still scarce in the field of depression. Well-conducted reviews have shown surprising heterogeneity and little consensus considering brain changes in the course of psychotherapy [35], [36], [37], [38], [39], [40]. For prefrontal metabolism, for instance, both increases and decreases have been reported after psychotherapy [37]. One good review comparing cognitive therapy and antidepressant medication proposes a promising model integrating findings and guiding future research to disentangle various brain changes [41]. When depression is associated with decreased prefrontal and increased amygdala function, antidepressant medication might directly decrease amygdala activity whereas cognitive therapy might lead to increased prefrontal function. With higher prefrontal activity, the amygdala can be more efficiently down-regulated in the further course, thus possibly explaining the more sustained effect of cognitive therapy.

Apart from applying longitudinal designs, another means to enhance the value of neuroimaging studies in depression is the combination of different imaging techniques and new ways to analyse fMRI data. With diffusion-tensor MRI (DTI), for instance, the fibres connecting active brain areas can be traced helping to disentangle the complex interactions between distant regions [42]. Analysis techniques like functional connectivity [43], [44] or dynamic causal modelling [43] might also help in the search for causal relations between corresponding brain areas. Finally, pattern classification [45], [46] is a promising and fresh approach to analyse fMRI data and might also contribute to the more profound understanding of the depressed brain.

## How to go beyond snapshots

In summary, the picture we have from the depressed brain is still far from being complete and homogenous. Promising theoretical models offer new possible explanations and can lead to advanced study designs, but empirical support for their hypotheses is still preliminary [18], [41]. Furthermore, a new wave of longitudinal studies points in the right direction to advance in the field, but their results are also inconclusive and they track patients typically only over a few months. We thus want to briefly comment on three issues that could, in our opinion, further increase the ecological value of neuroimaging research in depression. This commentary "How to go beyond snapshots" is hence about what patients to take a picture of, taking various pictures over the course of treatment and how to take clinically relevant pictures.

### What patients to take a picture of?

Larger sample sizes are needed to allow comparisons within patient groups. This, of course, requires patient selection based on thoroughly conducted diagnostics. If

we could go beyond purely syndrome-based diagnoses of depression and differentiate biologically-based illness subtypes, the homogeneity and reproducibility of studies could be enhanced [6].

### Take various pictures over the course of treatment.

Many published studies do not take into account that depressive symptoms change, though they do change: within a day, a year or the course of therapy. A single measurement cannot depict this variability. Future studies should include repeated brain measurements that extend over many months, ideally following the development of treatment or even tracking the state of remission. This could tackle the main shortcoming of many of the longitudinal studies that follow patients typically only over a few months. Which changes can then be expected? As mentioned above, due to compensatory brain mechanisms, it is unlikely that a successful improvement in depressive symptoms would result in brain activity that matches the pattern found in non-depressed controls. Thus, future research should go beyond a patient-control comparison. One way to examine compensatory mechanisms is to establish a link between external measurements of symptoms and changes in brain activation.

### How to take clinically relevant pictures

Future studies should always consider the highly individual nature of depression. The vast majority of research in this field uses stimuli that are adapted from designs in basic research on emotion processing, like faces or pictures [47], [48]. Those stimuli are relatively unspecific and bear limited relation to clinical features of depression. Additionally, individual differences in the personal relevance of such stimuli are not taken into account. One possible improvement could thus be the application of stimuli in the fMRI that are individually tailored and clinically derived for each patient. In our recent study we conducted clinical interviews following the system of operationalized psychodynamic diagnostics [49] to create sentences that describe each patients repetitive dysfunctional interpersonal relation in order to specifically activate one significant component leading to or maintaining their depression [50]. We believe that pictures taken in such a way for multiple times (in our study before psychotherapy and after 8 and 16 months of treatment) could provide a new way to go beyond snapshots.

## Notes

### Competing interests

The authors declare that they have no competing interests.

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**Corresponding author:**

PD Dr. Henrik Kessler  
 Universitätsklinik für Psychiatrie und Psychotherapie,  
 Abteilung Medizinische Psychologie,  
 Sigmund-Freud-Straße 25, 53105 Bonn  
 henrik.kessler@ukb.uni-bonn.de

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